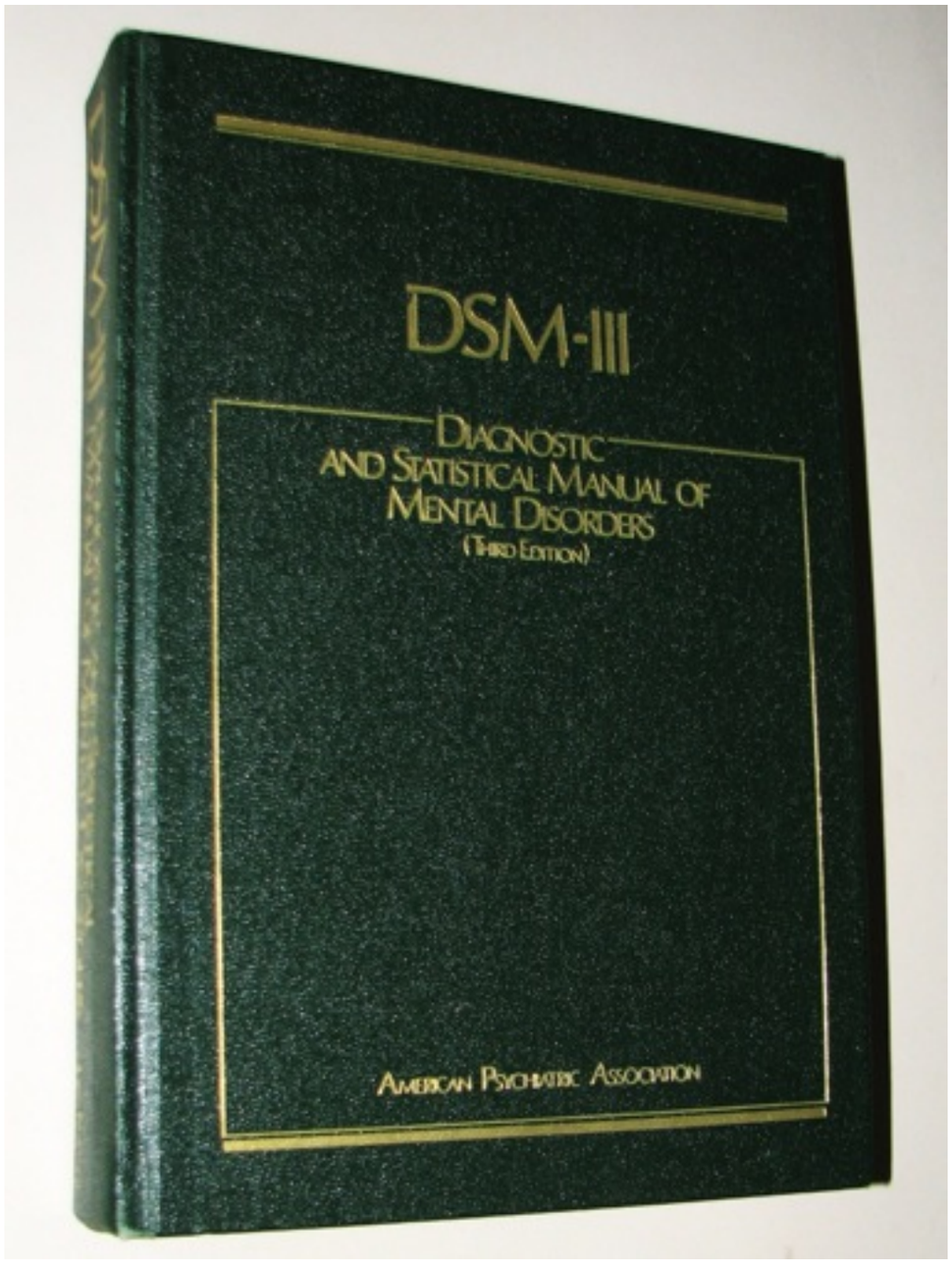
Anatomy of an Epidemic:

The History and Science of a Failed Paradigm of Care

Robert Whitaker
April 2016



DSM III was the "book that changed everything."

—Jeffrey Lieberman
American Psychiatric Association President

The Disease Model

"The major psychiatric illnesses are diseases. They should be considered medical illnesses, just as diabetes, heart disease, and cancer are." The thought was that each "different illness has a different specific cause . . . There are many hints that mental illness is due to chemical imbalances in the brain and that treatment involves correcting these chemical imbalances."

Nancy Andreasen
Editor-in-Chief of the *American Journal of Psychiatry*
The Broken Brain, 1984

Validating the Disease Model: The Chemical Imbalance Theory of Mental Disorders

1981: "Researchers believe clinical depression is caused by a chemical imbalance in the brain." University of Chicago psychiatrist Herbert Meltzer, in interview with Associated Press.

1988. Antidepressants "restore the chemical imbalance scientists have linked to many depressions." John Talbott, former president of the American Psychiatric Association (APA), in interview with the *St. Petersburg Times*.

2001: "We now know that mental illnesses--such as depression or schizophrenia--are not 'moral weaknesses' or 'imagined' but real diseases caused by abnormalities of brain structure and imbalances of chemicals in the brain." -- APA President Richard Harding, in article in *Family Circle* magazine.

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2001: Antidepressants "restore brain chemistry to normal." Future APA President Nada Stotland, in Family Circle magazine.

2005: A psychiatrist is a "specialist specifically trained to diagnose and treat chemical imbalances."--APA press release.

2005: "Antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain." APA's "Let's Talk Facts About Depression" brochure.

2014: "Research has shown that imbalance in neurotransmitters like serotonin, dopamine and norepinephrine can be corrected with antidepressants." --National Alliance on Mental Illness.

The Public Believes

In a 2006 survey:

- 87 percent of Americans said they now knew that schizophrenia was caused by a chemical imbalance.
- 80 percent of Americans said they now knew that depression was caused by a chemical imbalance.

What Science Revealed About the Low Serotonin Theory of Depression

"Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression."

--NIMH, 1984

J. Maas, "Pretreatment neurotransmitter metabolite levels and response to tricyclic antidepressant drugs." *Am J Psychiatry* 141 (1984): 1159–71.

"There is no clear and convincing evidence that a monoamine deficiency accounts for depression; that is, there is no real monoamine deficit."

--Stephen Stahl, *Essential Psychopharmacology*, 2000

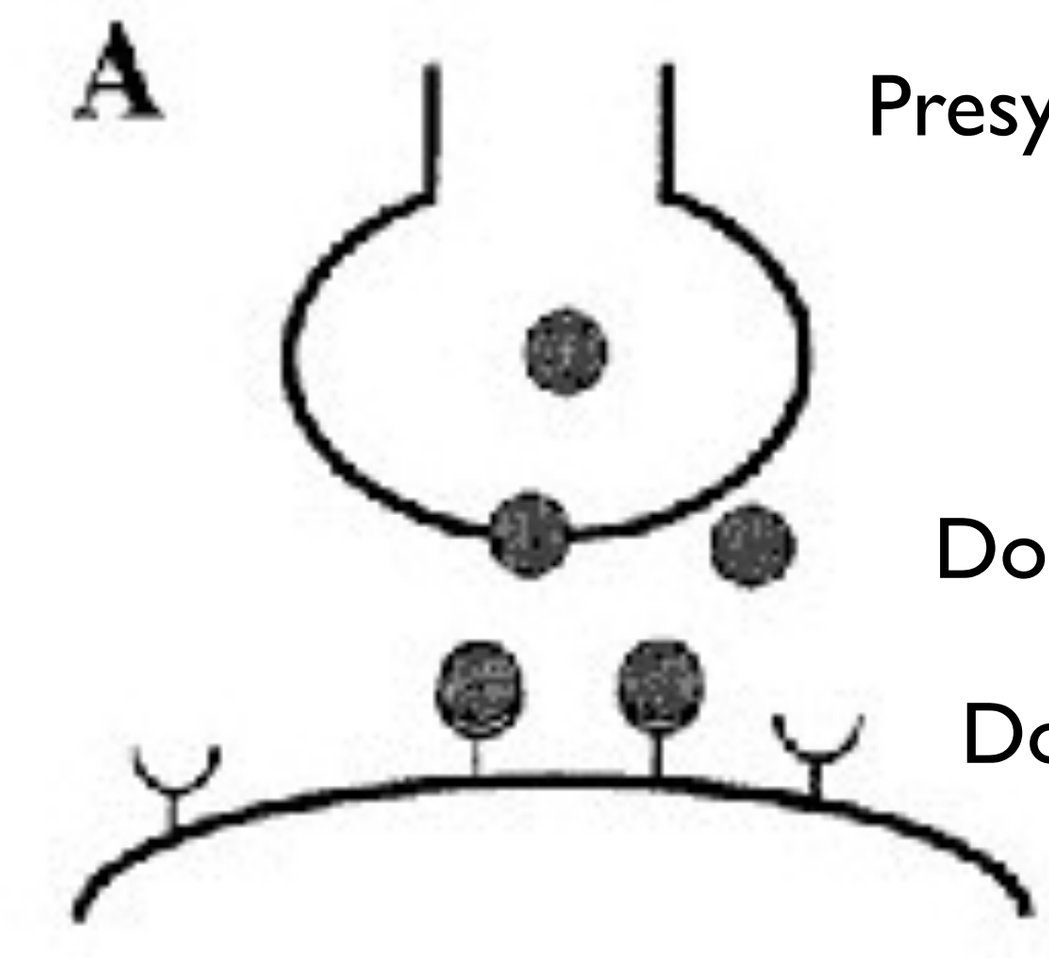
The Scientific Conclusion

"We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them."

--Kenneth Kendler, *Psychological Medicine*, 2005

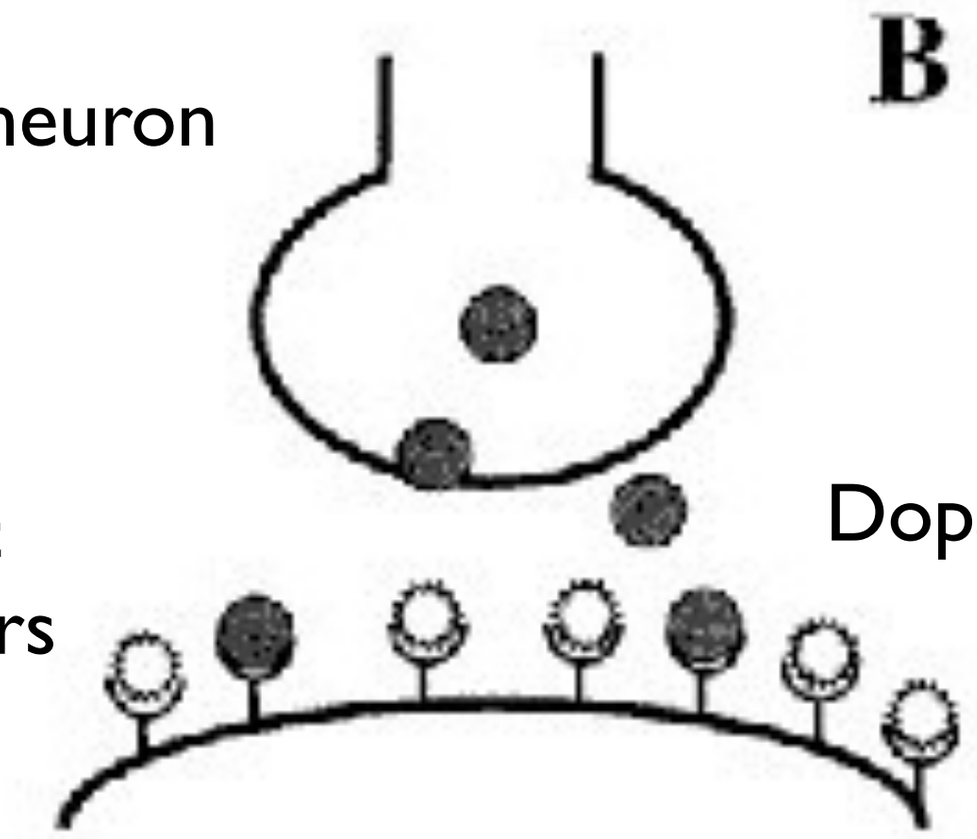
And Now for the Rest of the Story: Drug-Induced Oppositional Tolerance

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

Presynaptic neuron



Antipsychotic
blocks receptors

Dopamine

Postsynaptic neuron

Brain increases
receptors to
compensate for
drug blockade

A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

- Psychiatric medications "create perturbations in neurotransmitter functions."

- In response, the brain goes through a series of compensatory adaptations in order "to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu."

- The "chronic administration" of the drugs then cause "substantial and long-lasting alterations in neural function."

- After a few weeks, the person's brain is now functioning in a manner that is "qualitatively as well as quantitatively different from the normal state."

Source: Hyman, S. "Initiation and adaptation: A paradigm for understanding psychotropic drug action." *Am J Psychiatry* 153 (1996):151-61.

The Possible Consequences of "Oppositional Tolerance"

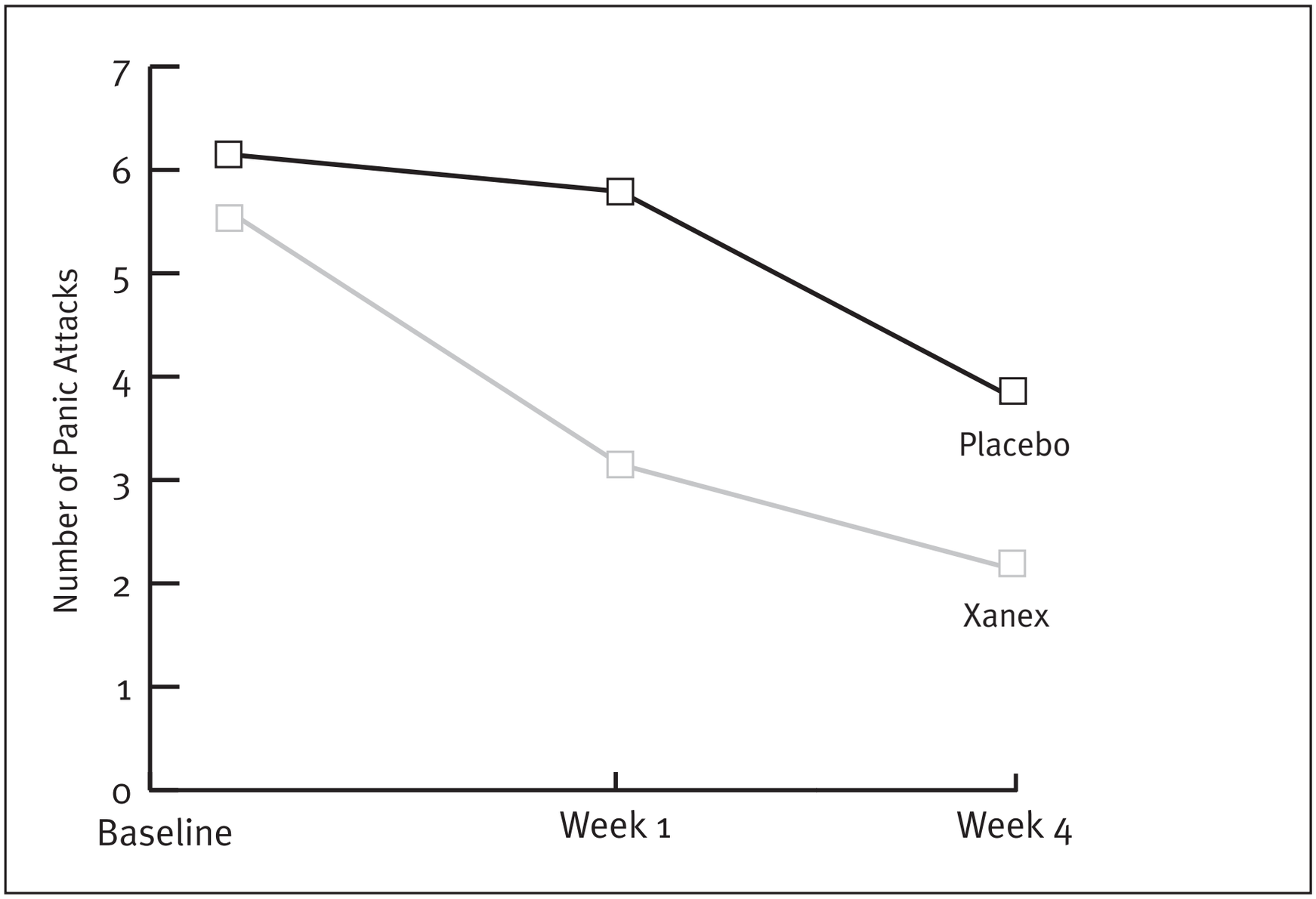
"Continued drug treatment may induce processes that are the opposite of what the medication originally produced." This may "cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible."

-Rif El-Mallakh, University of Louisville, 2011

Source: El-Mallakh, R. "Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. *Medical Hypotheses* 76 (2011): 769-773.

The Testing of Xanax for Panic Disorder (1980s)

The Xanax Investigators Used This Data to Report Efficacy



Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22.

The Conclusion in the Literature

The study provides a "demonstration of the efficacy of alprazolam compared with placebo in the short-term treatment of panic disorder."

—Gerald Klerman
Archives of General Psychiatry

G. Klerman. "Overview of the cross-national collaborative panic study." *Arch Gen Psychiatry* 45 (1988): 407–412.

Here is What the Press Reported

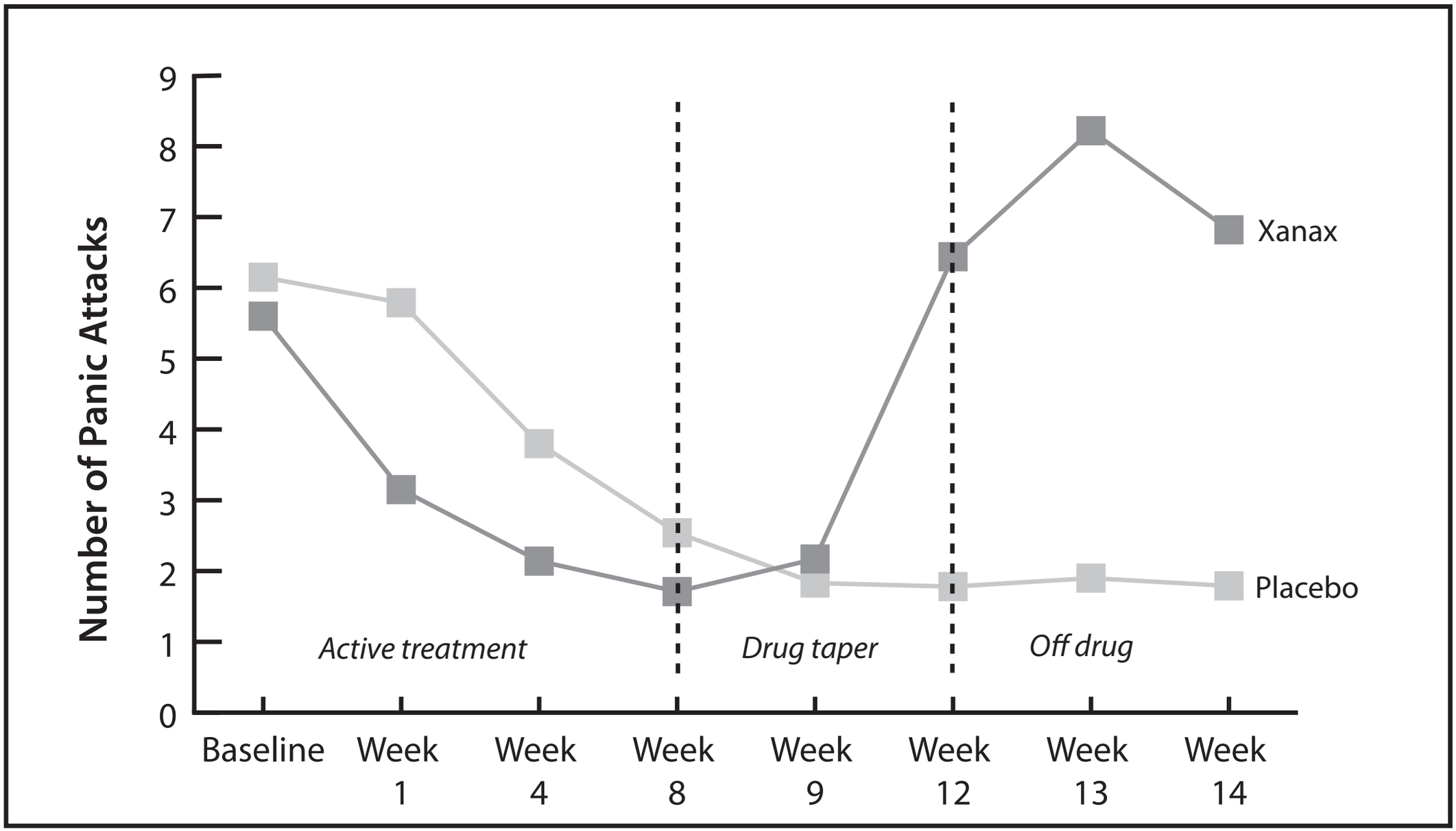
Headline in Newspaper: "In a Panic? Help Is On the Way."

Xanax, the paper reported, works for "70 percent to 90 percent" of those who suffer from the illness.

St. Louis Post-Dispatch, October 7, 1990

Here Are the Actual Study Results

The Xanax Study



Source: Ballenger, C. "Alprazolam in panic disorder and agoraphobia." *Arch Gen Psychiatry* 45 (1988):413-22.
Pecknold, C. "Alprazolam in panic disorder and agoraphobia." *Arch Gen Psychiatry* 45 (1988):429-36.

The Long-term Effects of Antidepressants

The Hippocratic Oath

In order for a treatment to do no harm, it must improve on natural recovery rates.

Long-term Outcomes in the Pre-Antidepressant Era

• Emil Kraepelin, 1921. Sixty percent of 450 patients hospitalized for an initial bout of depression experienced but a single bout of the illness, and only 13% had three or more episodes in their lives.

• Horatio Pollock, New York State, 1931. In a long-term study of 2700 first-episode depressed patients, more than half never had another bout of depression that required hospitalization, and only 13% had three or more episodes.

• Gunnar Lundquist, Sweden, 1945. In an 18-year study of 216 patients, 49% had only a single episode, and another 21% had only one other episode.

"Assurance can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course."

--George Winokur, Washington University,
Manic Depressive Illness, 1969

Clinical Perceptions in Early Years of Antidepressant Use

- H.P. Hoheisel, German physician, 1966: Exposure to antidepressants appeared to be "shortening the intervals" between depressive episodes.

- Nikola Schipkowensky, Bulgarian psychiatrist, 1970: The antidepressants were inducing "a change to a more chronic course."

Source: Van Scheyen, J.D. "Recurrent vital depressions," *Psychiatria, Neurologia, Neurochirurgia* 76 (1973):93-112.

The Chronicity Worry is Tested

J.D. Van Scheyen, Dutch psychiatry, 1973:

After conducting a study of 94 depressed patients, he concluded that "it was evident, particularly in the female patients, that more systematic long-term antidepressant medication, with or without ECT [electronconvulsive therapy], exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate and a decrease in cycle duration . . . Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?"

An Episodic Illness Turns Chronic in the Antidepressant Era

National Institute of Mental Health Panel on mood disorders, 1985:

"Improved approaches to the description and classification of [mood] disorders and new epidemiologic studies [have] demonstrated the recurrent and chronic nature of these illnesses, and the extent to which they represent a continual source of distress and dysfunction for affected individuals."

High-Relapse Rates Following Antidepressant Use

In a 1997 meta-analysis, Harvard researchers report that 50% of all drug-withdrawn patients relapsed within 14 months. They also noted that the longer the patient had been on an antidepressant prior to drug withdrawal, the higher the relapse rate.

(In the pre-antidepressant era, this was the relapse rate seen in studies that lasted 15 years or more.)

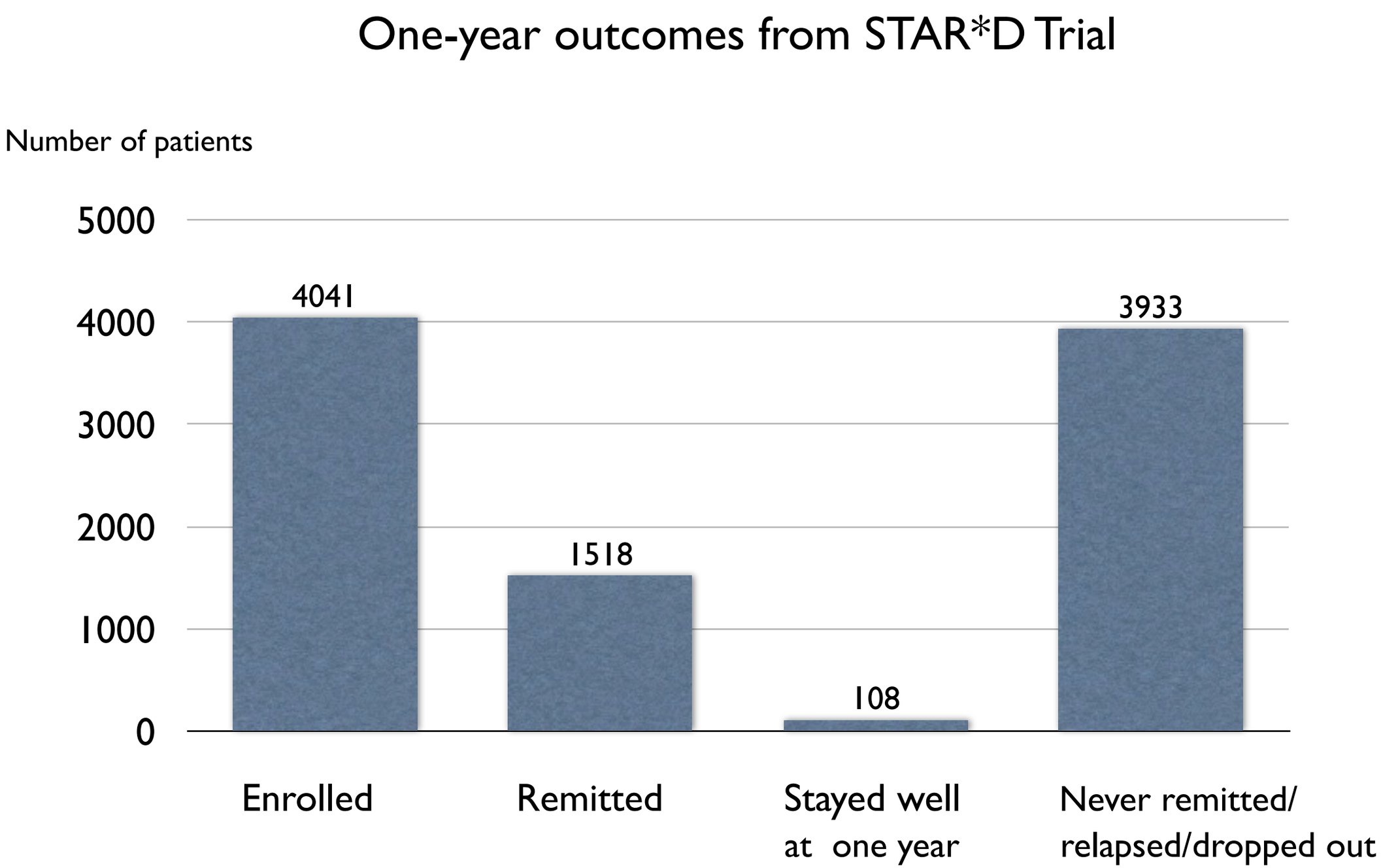
Source: Viguera, A. "Discontinuing antidepressant treatment in major depression," *Harvard Review of Psychiatry* 5 (1998):293-305.

The APA Acknowledges Change in Course of Depression in Modern Era

American Psychiatric Association's Textbook of Psychiatry, 1999:

It used to be believed that "most patients would eventually recover from a major depressive episode. However, more extensive studies have disproved this assumption." It was now known that "depression is a highly recurrent and pernicious disorder."

Depression Runs a Chronic Course Today



Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

Outcomes in Real-World Patients

In a 2004, NIMH-funded study:

•126 patients were treated with antidepressants and given emotional and clinical support "specifically designed to maximize clinical outcomes."

• Only 26% responded to antidepressants (50% reduction in symptoms).

• Only half of those who responded stayed better for a significant period of time

• Only 6% remitted and then remained in remission at the end of one year.

Source: J. Rush. "One-year clinical outcomes of depressed public sector outpatients," *Biological Psychiatry* 56 (2004):46-53.

"These findings reveal remarkably low response and remission rates."

--John Rush, 2004

Outcomes in Minnesota

In 2009, only 1,131 of 23,887 patients treated for major depression or dysthmia were in remission at the end of one year.

Source: MN Community Measures, *2010 Health Care Quality Report*

The Course of Medicated Depression Today

According to mainstream texts:

- One-third of all unipolar patients are non-responders to antidepressants. This group goes on to have a chronic course.

- Another third are partial responders. However, "resolution of major depressive episode with residual subthreshold depressive symptoms, even the first lifetime episode, appears to be the first step of a more severe, relapsing, and chronic future course."

- The final third of patients see their symptoms remit over the short term. About half of this group, when maintained on an antidepressant, stay well for long periods of time.

"Only 15% of people with unipolar depression experience a single bout of the illness," and for the remaining 85%, with each new episode, remissions become "less complete and new recurrences develop with less provocation."

--American Psychiatric Association Textbook, 1999

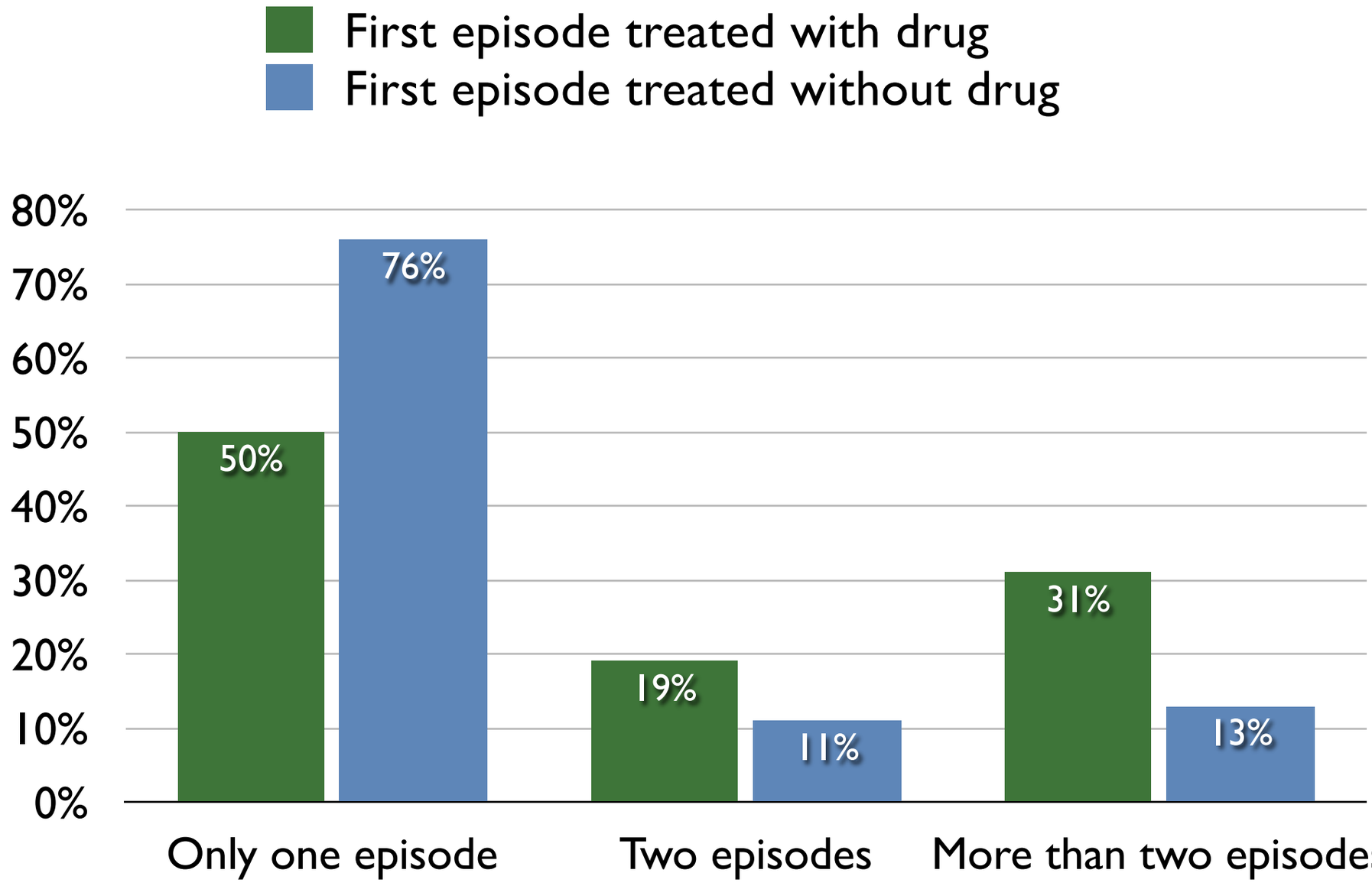
Are Antidepressants Depressogenic Over the Long-Term?

"Antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression . . . Use of antidepressant drugs may propel the illness to a more malignant and treatment unresponsive course."

--Giovanni Fava, *Psychotherapy and Psychosomatics*, 1995

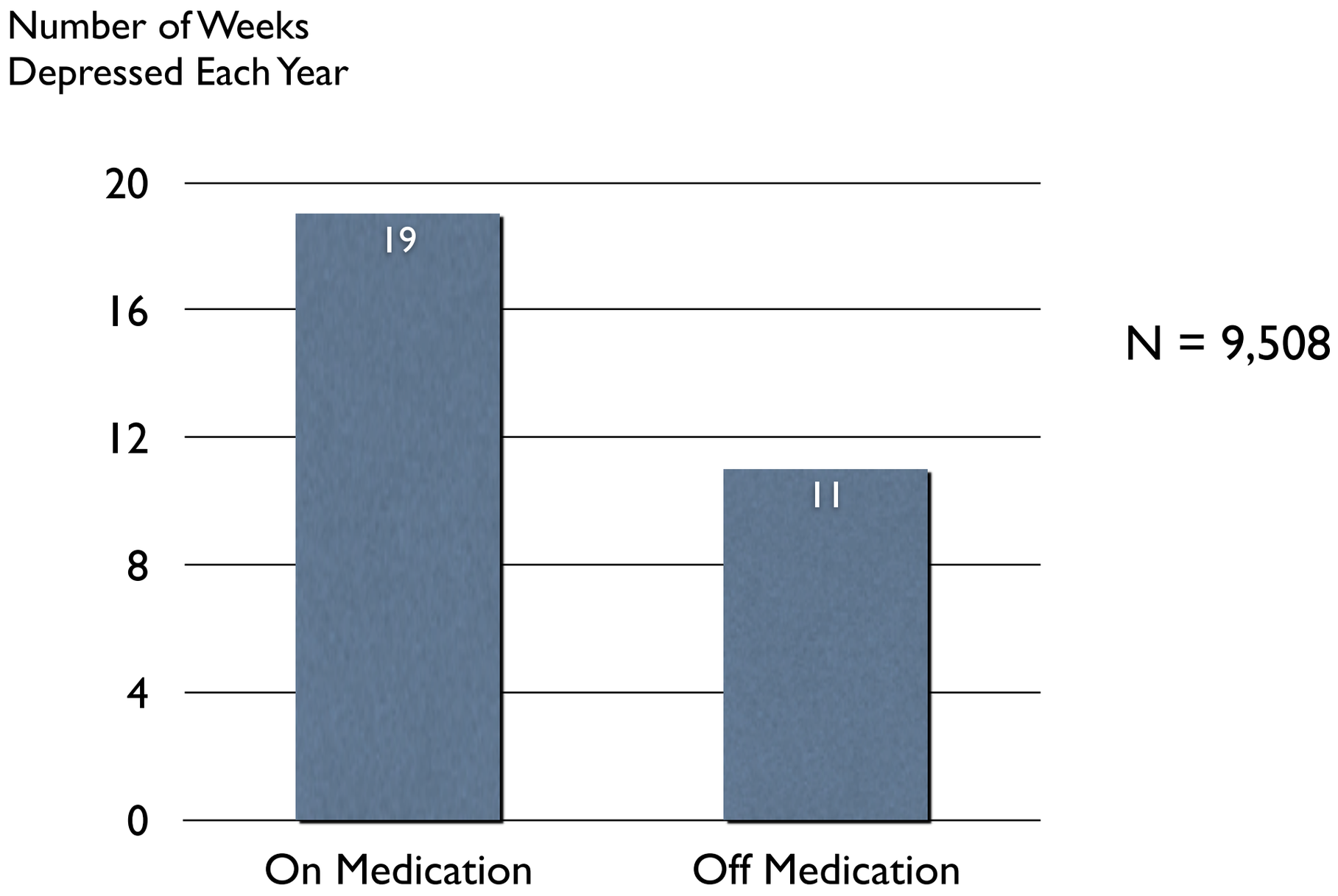
Depression in the Netherlands

(Over the course of ten years)



Source: E. Weel-Baumgarten, "Treatment of depression related to recurrence," *J Clin Psychiatry & Therapeutics* 25 (2000):61-66.

Five-Year Outcomes in Canada

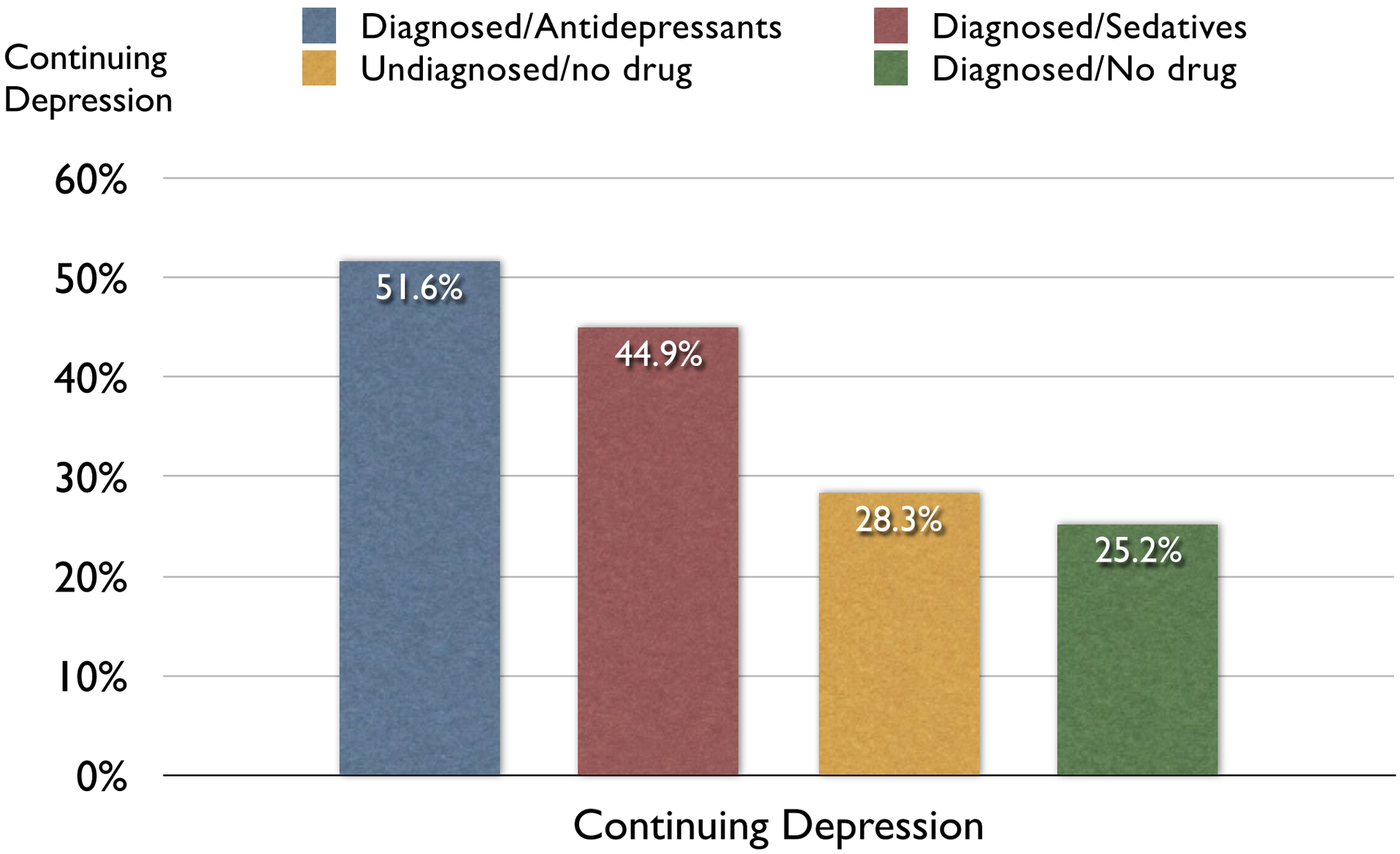


Source: S. Patten, "The Impact of antidepressant treatment on population health." *Population Health Metrics* 2 (2004): 9.

These findings are consistent with Giovanni Fava's hypothesis that "antidepressant treatment may lead to a deterioration in the long-term course of mood disorders."

--Scott Patten

One-Year Outcomes in WHO Screening Study for Depression



Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

"Patients not given drugs had milder illnesses but did significantly better than those receiving drugs, both in terms of symptoms lost and their diagnostic status." This was so "even after adjustment for initial scores on each instrument."

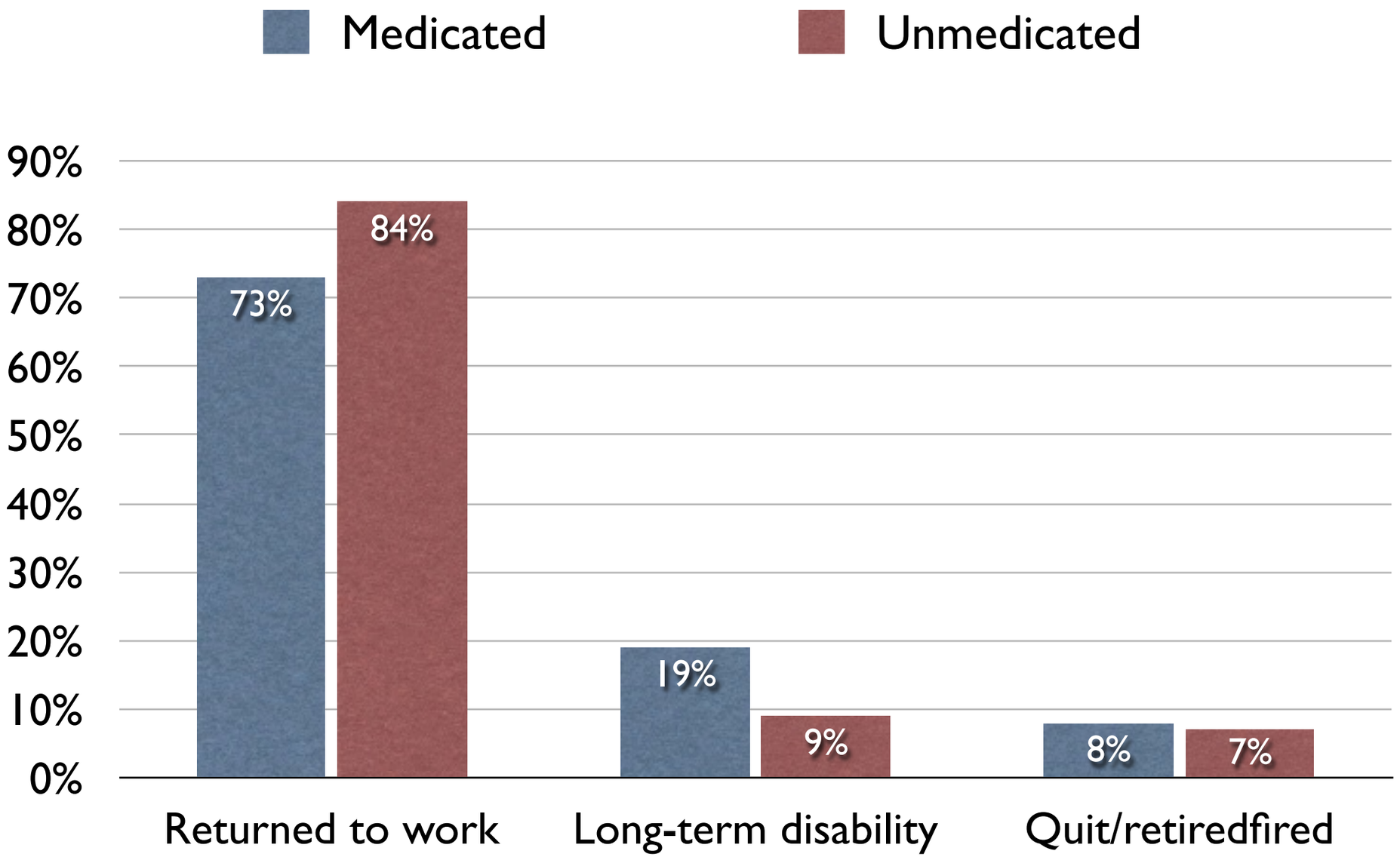
--D. Goldberg

Antidepressants Lessen the Long-Term Benefits of Exercise

Treatment during first 16 weeks	Percentage of patients in remission at end of 16 weeks	Percentage of patents who relapsed in following six months	Percentage of all patients depressed at end of ten months
Zoloft alone	69%	38%	52%
Zoloft plus exercise	66%	31%	55%
Exercise alone	60%	8%	30%

Source: Babyak, M. "Exercise treatment for major depression." *Psychosomatic Medicine* 62 (2000):633-8.

Canadian Study of Risk of Long-term Disability for Depressed Workers

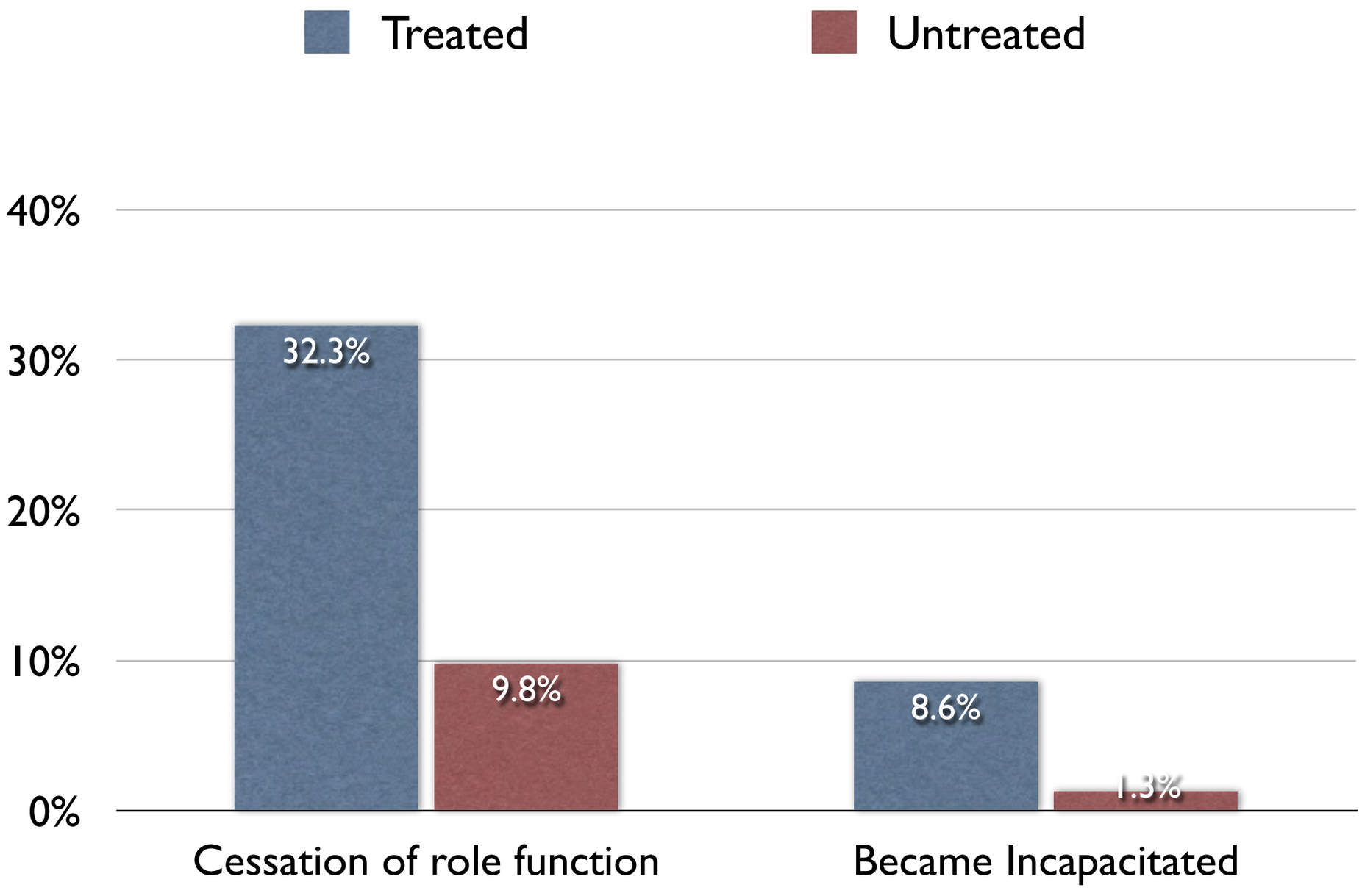


Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.

"Does the lack of antidepressant use reflect a resistance to adopting a sick role and consequently a more rapid return to work?"

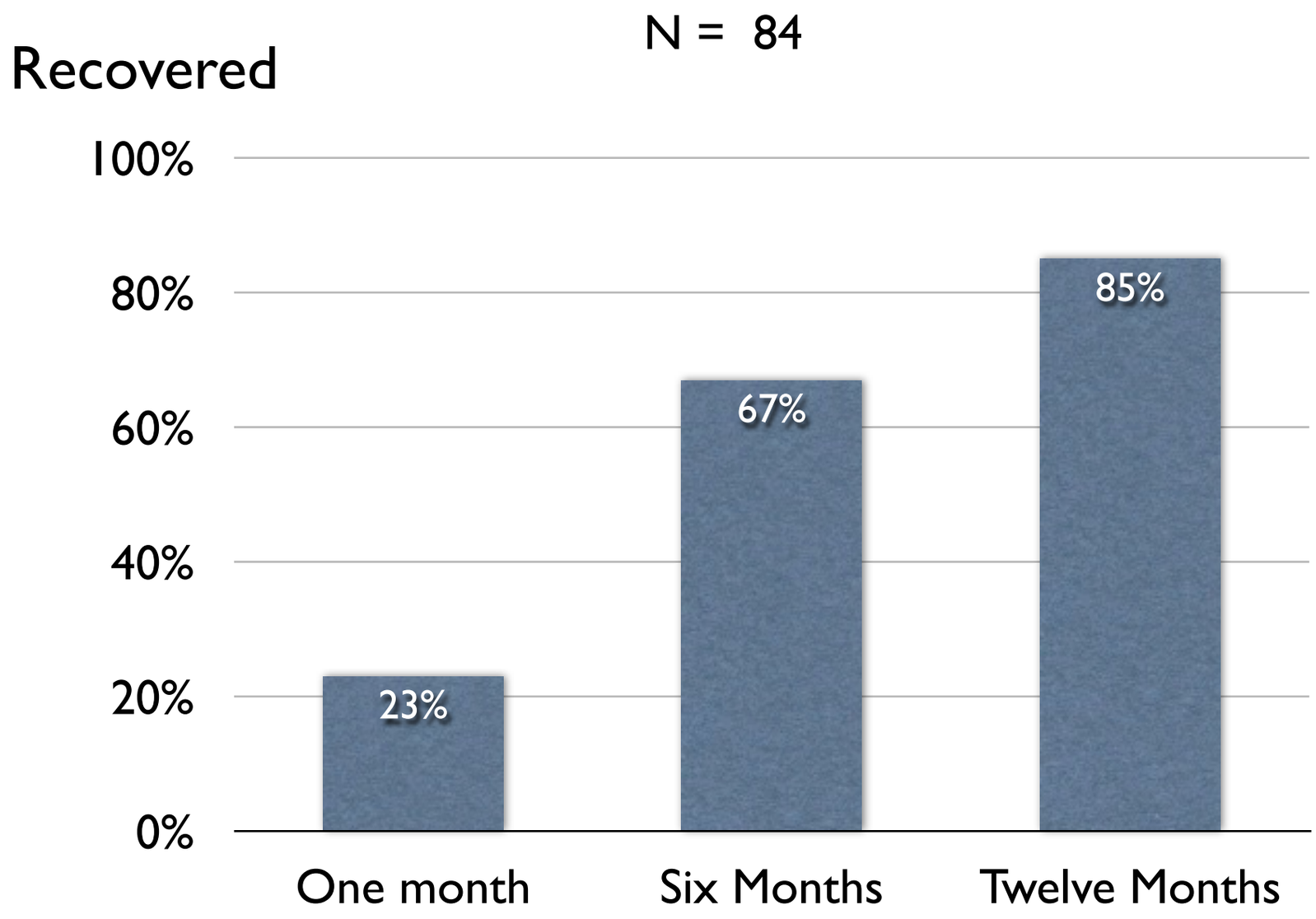
--Carolyn Dewa

NIMH's Study of Untreated Depression



Source: W. Coryell. "Characteristics and significance of untreated major depressive disorder." *American Journal of Psychiatry* 152 (1995):1124-29.

One-Year Recovery Rates in NIMH-Funded Study of Unmedicated Depression



Source: M. Posternak, "The naturalistic course of unipolar major depression in the absence of somatic therapy." *Journal of Nervous and Mental Disease* 194 (2006):324-349.

"If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this."

--Michael Posternak

A Biological Explanation for Why Antidepressants May Be Depressogenic Agents Over the Long-Term

The Problem

- Over time, antidepressants induce brain changes that "are the opposite of what the the medication originally produced." Rather than raise serotonin levels, the drugs over the long-term impair serotonergic pathways in the brain.

Animal Evidence

- In studies with rats, long-term treatment with an SSRI led to markedly reduced serotonin in "nine areas of the brain." In addition, treatment with an SSRI leads to a reduced density of receptors for serotonin in the brain.

- In experiments with animals, such impairments in serotonergic functions are "associated with increased depressive and anxious behaviors."

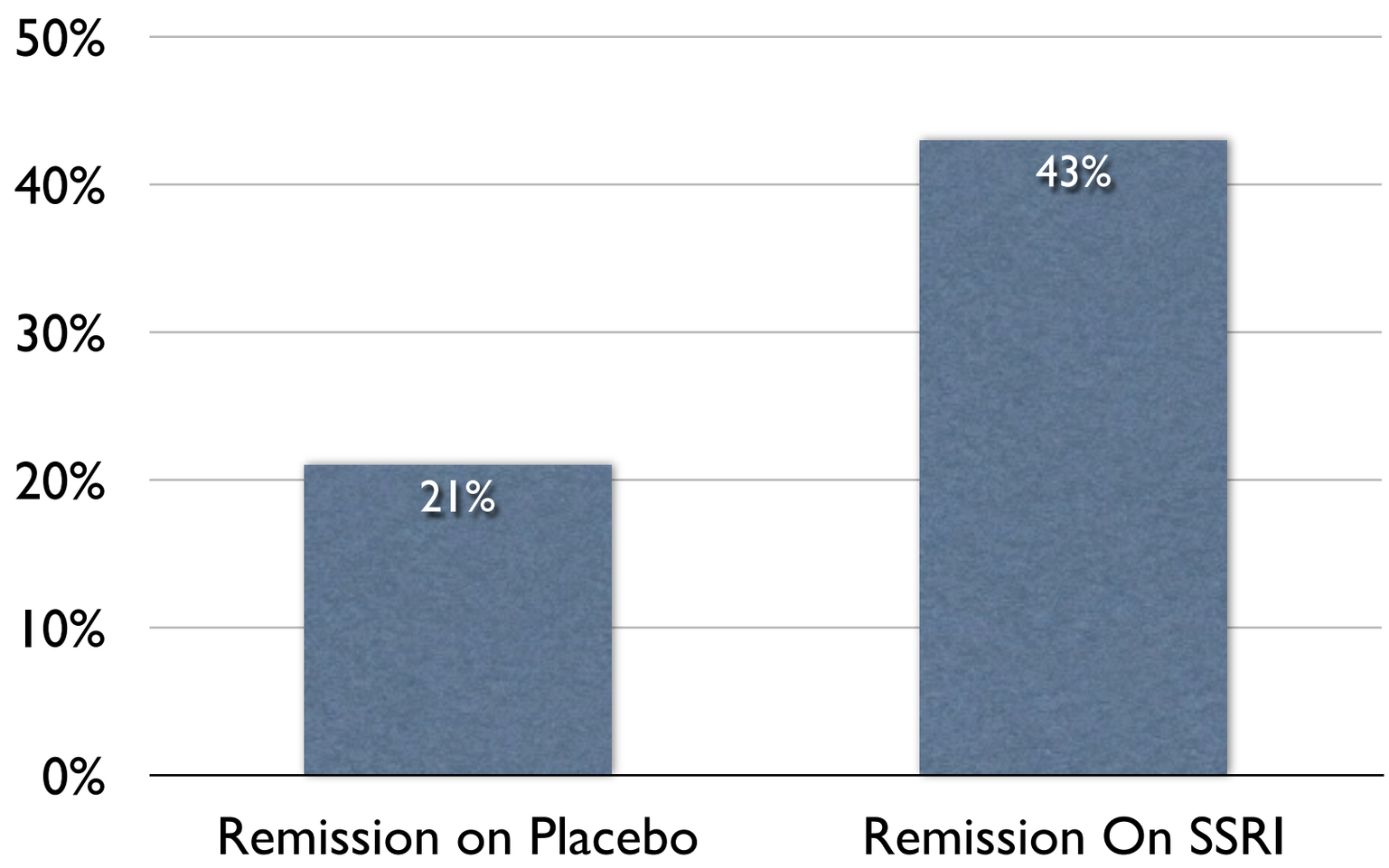
Source: El-Mallakh, R. "Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. *Medical Hypotheses* 76 (2011): 769-773.

"When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible."

Giovanni Fava, 2011

Source: G. Fava. "The mechanisms of tolerance in antidepressant action." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35 (2011): 1593-1602.

Three-Month Risk of Relapse After Initial Remission: Placebo vs. SSRI-Withdrawn Patients

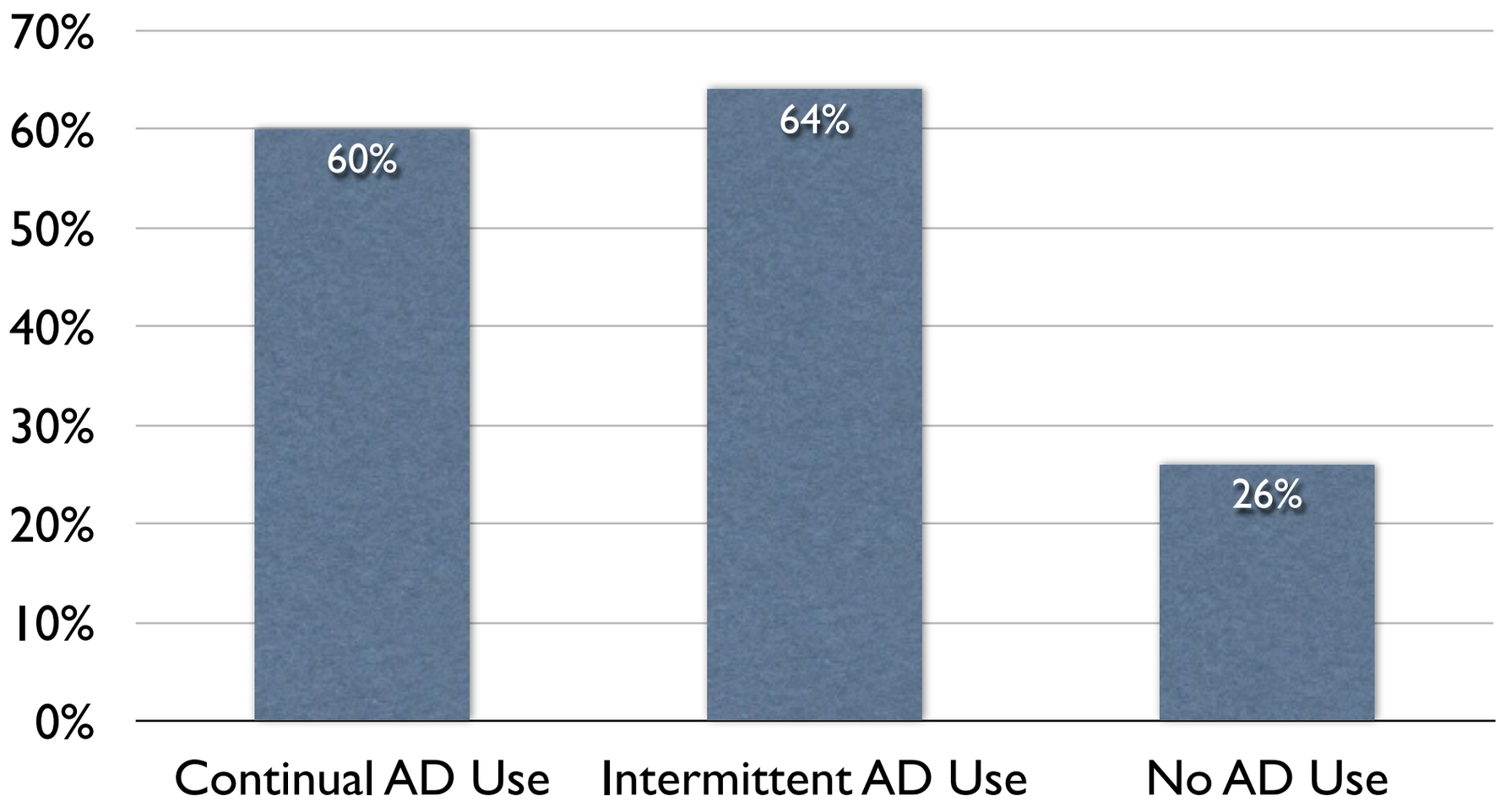


P. Andrews: "Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good." Frontiers in Psychology 3 (2012): 1-18.

"The more antidepressants perturb monamine levels in the brain, the more the brain appears to push back, which increases the risk of relapse when the drug is discontinued . . . antidepressant use appears to increase [biological] susceptibility to depression."

--Paul Andrews, 2012

Two-Year Relapse Rates for Remitted Patients in the Netherlands



Source: C. Bockting. "Continuation and maintenance use of antidepressants in recurrent depression." *Psychotherapy and Psychosomatics* 77 (2008): 17-26.

"Continued antidepressant treatment may oppose the initial acute effects of [the] antidepressant . . . neurobiological mechanism(s) may be involved in increasing vulnerability" to relapse.

--C. Bockting, 2008

Tardive Dysphoria

"A chronic and treatment-resistant depressive state is proposed to occur in individuals who are exposed to potent antagonists of serotonin reuptake pumps (i.e. SSRIs) for prolonged time periods. Due to the delay in the onset of this chronic depressive state, it is labeled tardive dysphoria. Tardive dysphoria manifests as a chronic dysphoric state that is initially transiently relieved by -- but ultimately becomes unresponsive to -- antidepressant medication. Serotonergic antidepressants may be of particular importance in the development of tardive dysphoria."

-- Rif El-Mallakh, 2011

Source: El-Mallakh, R. "Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. *Medical Hypotheses* 76 (2011): 769-773.

The Antidepressant Pathway to Bipolar

In 2004, Yale University investigators reviewed the records of 87,290 patients diagnosed with depression or anxiety between 1997 and 2001, and those treated with an antidepressant converted to bipolar at the rate of 7.7% per year, which was three times greater than those not exposed to the drugs. As a result, 20 to 40% of unipolar depressed patients in the U.S. who stay on antidepressants long-term convert to bipolar illness.

Source: A. Martin. "Age effects on antidepressant-induced manic conversion," *Arch of Pediatrics & Adolescent Medicine* 158 (2002):773-80.

Fred Goodwin, former director of the National Institute of Mental Health, 2005:

"If you create iatrogenically a bipolar patient, that patient is likely to have recurrences of bipolar illness even if the offending antidepressant is discontinued. The evidence shows that once a patient has had a manic episode, he or she is more likely to have another one, even without the antidepressant stimulation."

Acknowledgement That Bipolar Outcomes Have Worsened in Modern Era

Carlos Zarate, head of NIMH Mood Disorders Program, 2000:

"In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment."

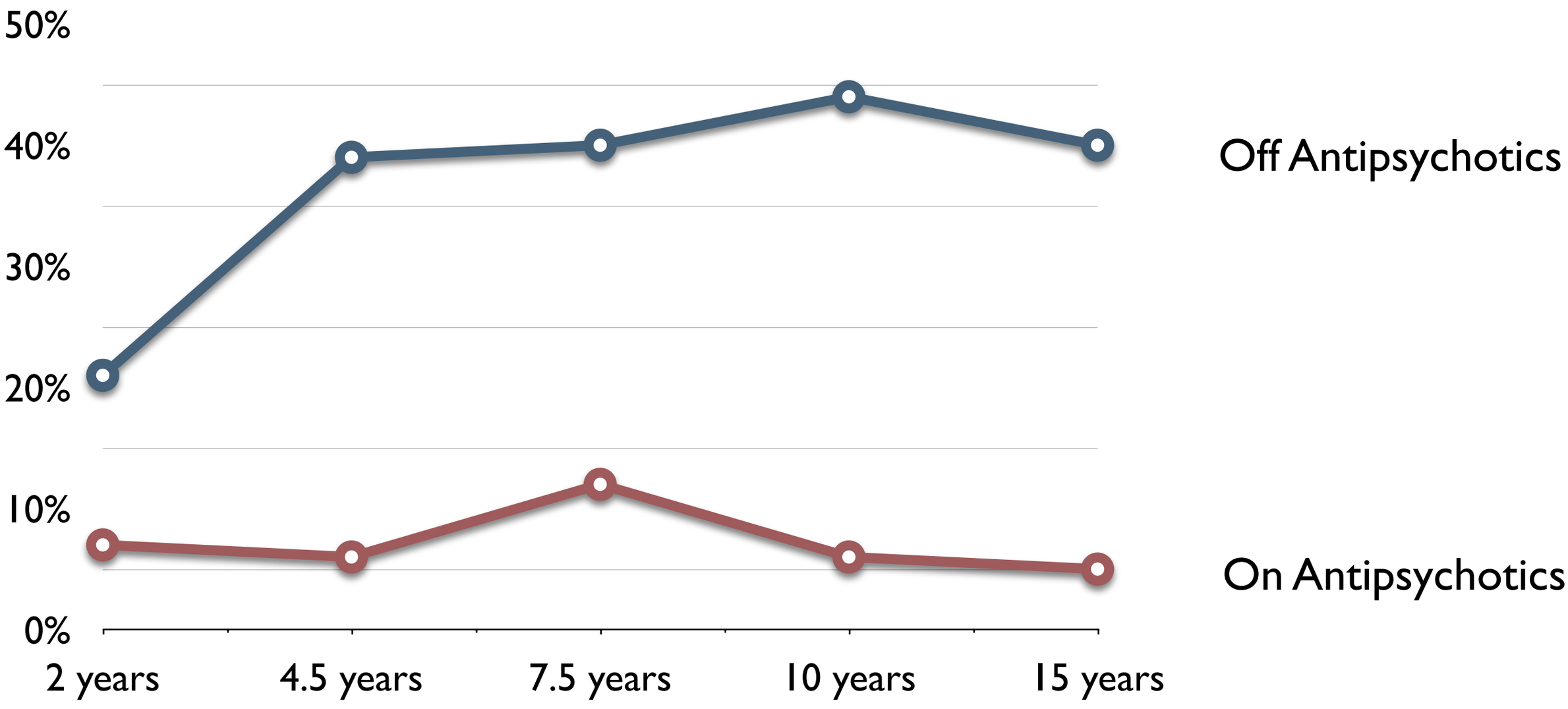
Ross Baldessarini, Harvard Medical School, 2007.

"Prognosis for bipolar disorder was once considered relatively favorable, but contemporary findings suggest that disability and poor outcomes are prevalent, despite major therapeutic advances."

Fred Goodwin, 2008

"The illness has been altered. Today we have a lot more rapid cycling than we described in the first edition [of his book, *Manic Depressive Illness*], a lot more mixed states than we described in the first edition, a lot more lithium resistance, and a lot more lithium treatment failure than we described in the first edition. The illness is not what Kraepelin described any more."

Long-term Recovery Rates for Schizophrenia Patients



Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

"I conclude that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics."

--Martin Harrow, American Psychiatric Association annual meeting, 2008

Results from NIMH's Long-term Study of ADHD

At three years

"Medication use was a significant marker not of beneficial outcome, but of deterioration. That is, participants using medication in the 24-to-36 month period actually showed increased symptomatology during that interval relative to those not taking medication." Medicated children were also slightly smaller, and had higher delinquency scores.

At six years

Medication use was "associated with worse hyperactivity-impulsivity and oppositional defiant disorder symptoms," and with greater "overall functional impairment."

Source: Jensen, "A 3-year follow-up of the NIMH MTA study," *J Amer Academy of Child & Adolescent Psychiatry* 46 (200&):989-1002. Molina, "MTA at 8 years," J Amer Academy of Child & Adolescent Psychiatry 48 (2009): 484-500.

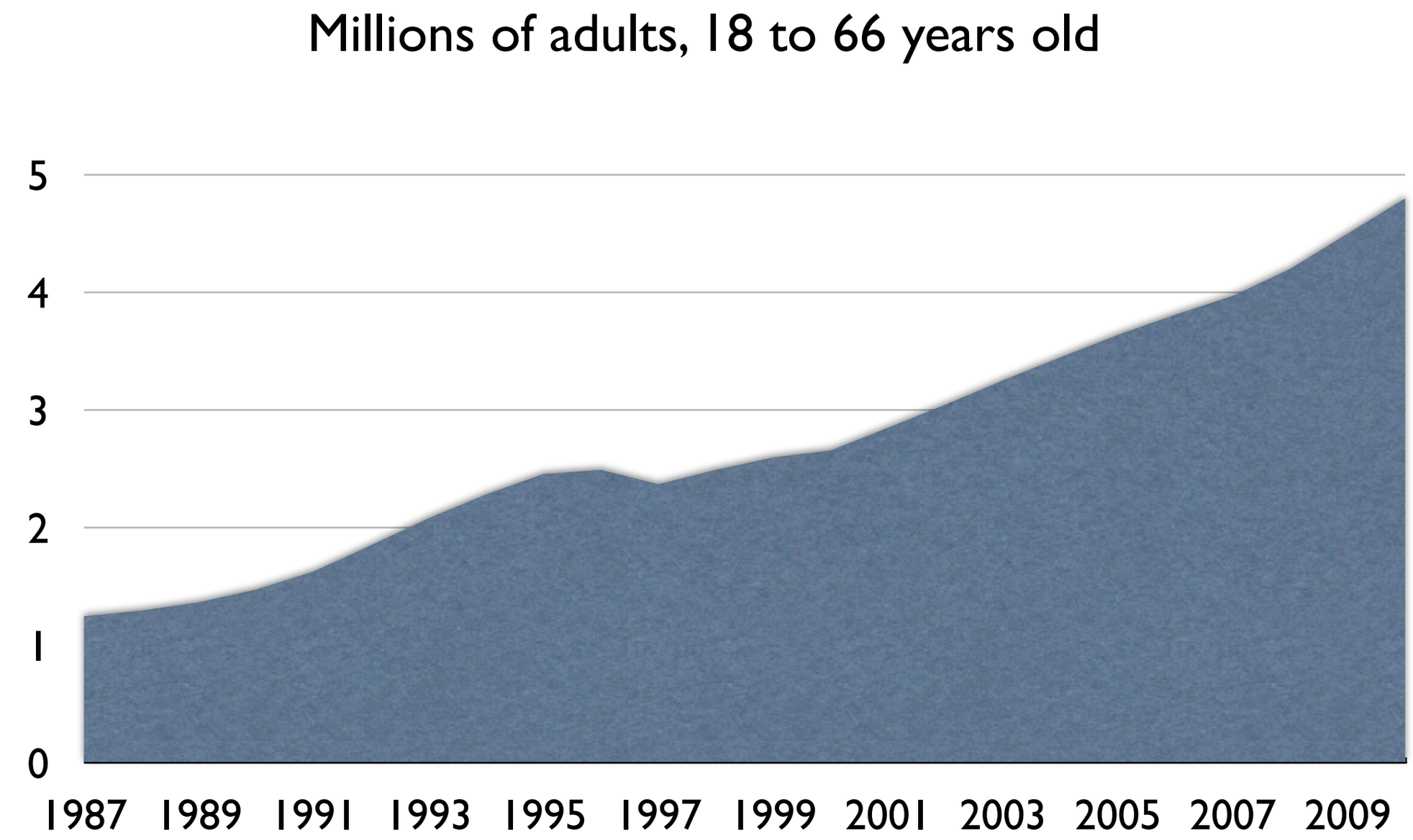
From the Co-founder of the Cochrane Collaboration:

"I know some excellent psychiatrists who help their patients a lot . . .I also know that some drugs can be helpful sometimes for some patients. And I am not 'antipsychiatry' in any way. But my studies in this area lead me to a very uncomfortable conclusion:

Our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good."

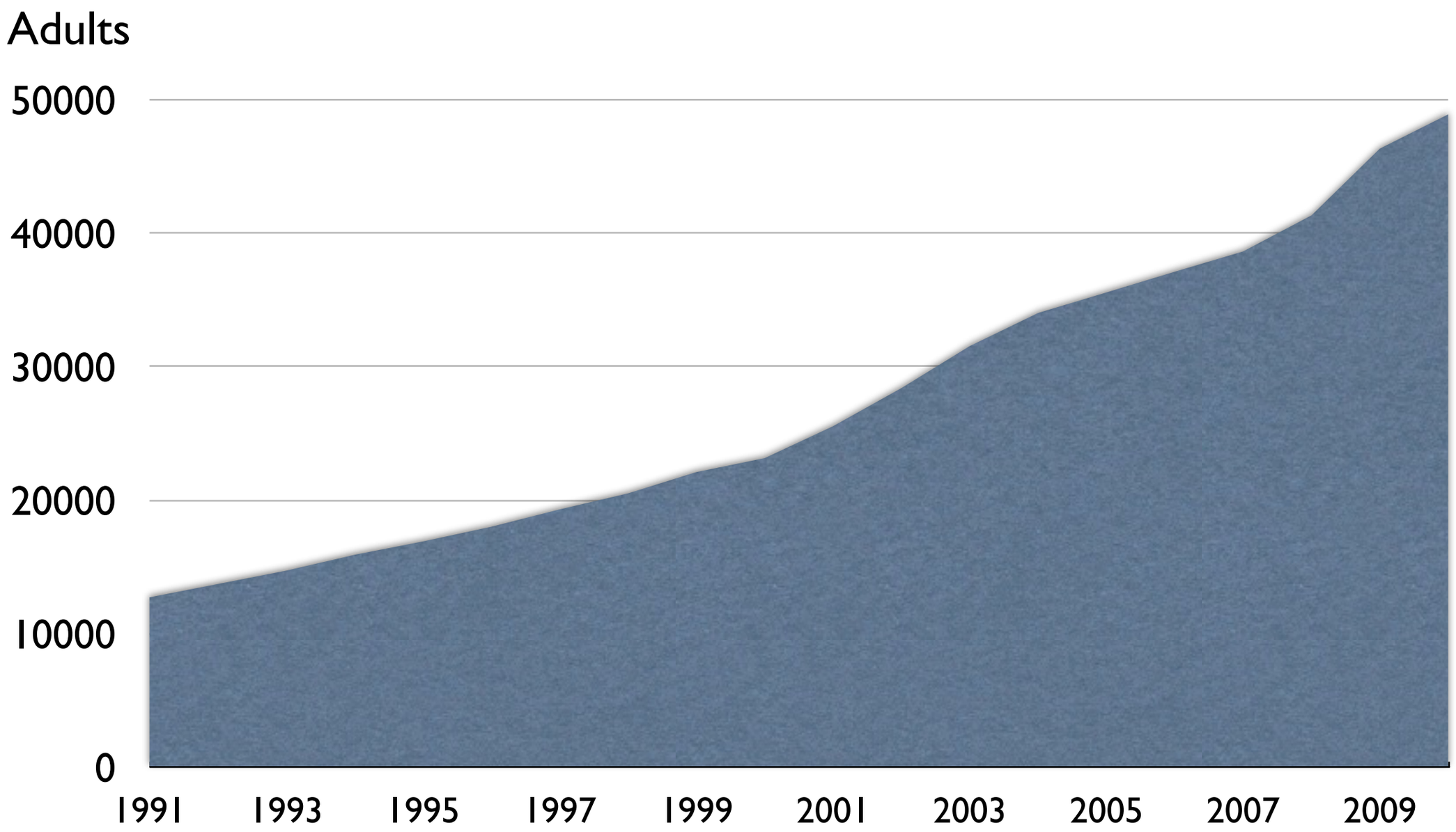
--Peter C. Gøtzsche, 2013
Co-founder of the Cochrane Collaboration
Director of the Nordic Cochrane Center

U.S. Disability in the Prozac Era



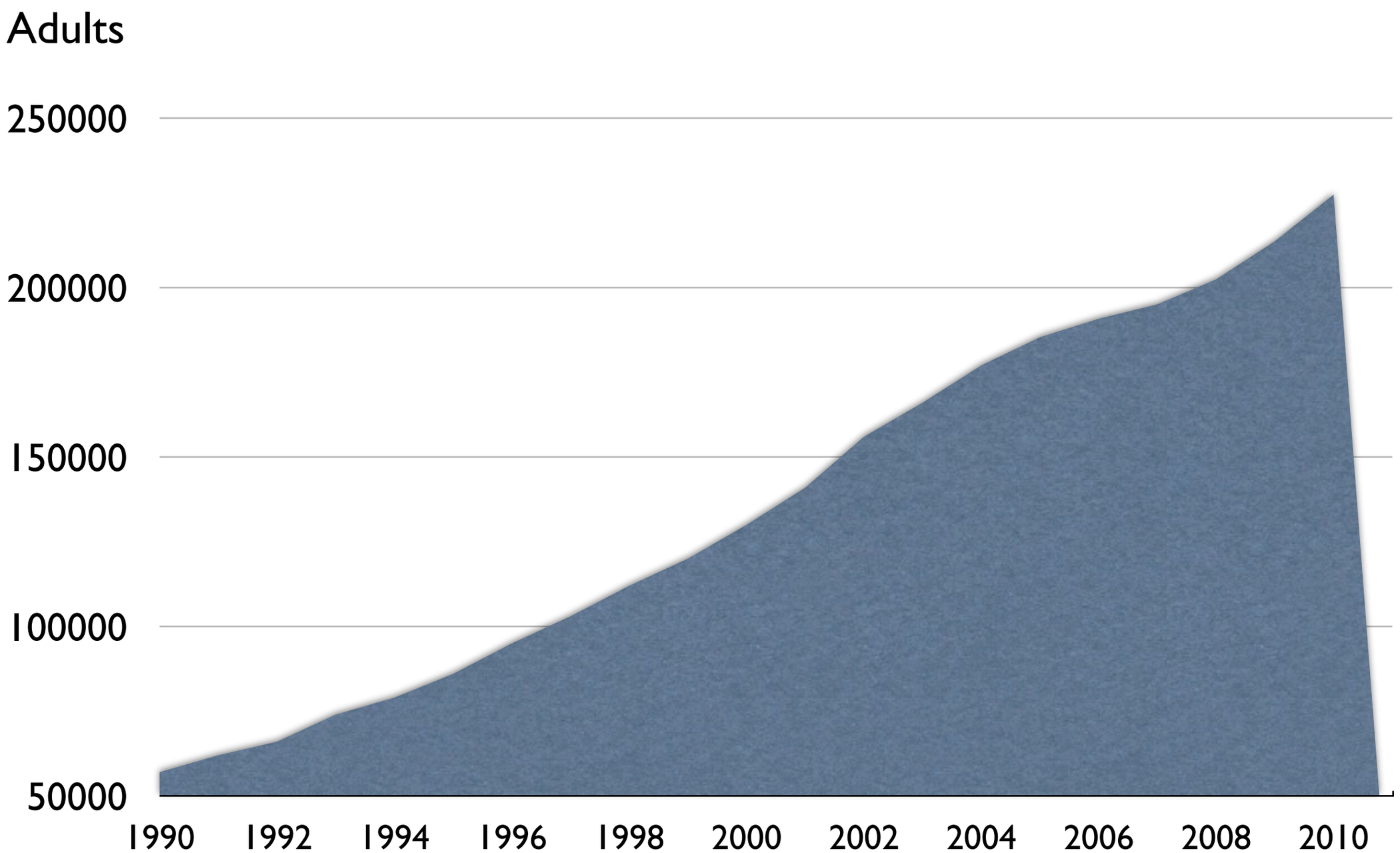
Source: U.S. Social Security Administration Reports, 1987-2010

Disability Due to Psychiatric Disorders in New Zealand, 1991-2010



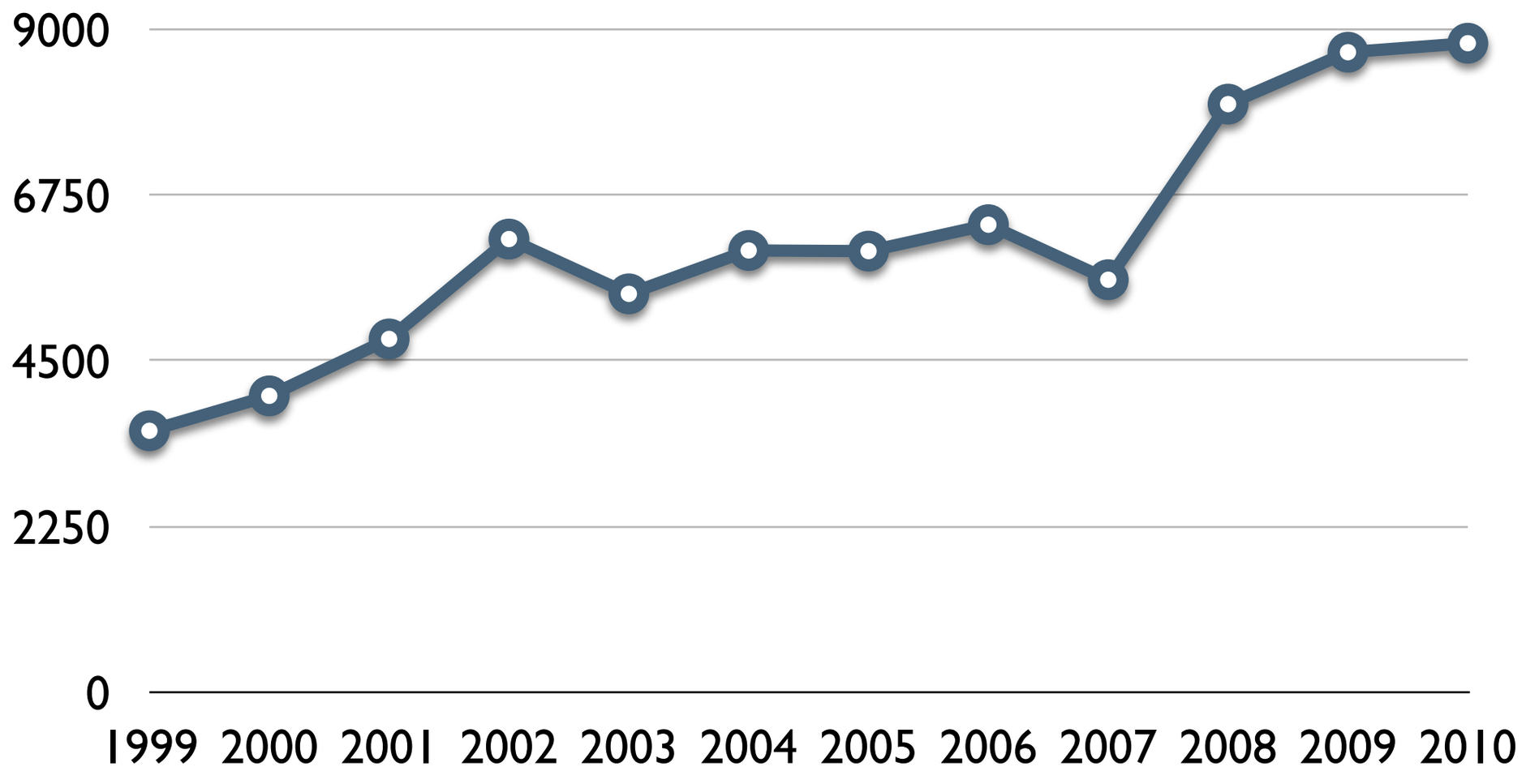
Source: *Statistics New Zealand,* Annual reports, 1999-2010

Disability Due to Psychiatric Disorders in Australia, 1990-2010



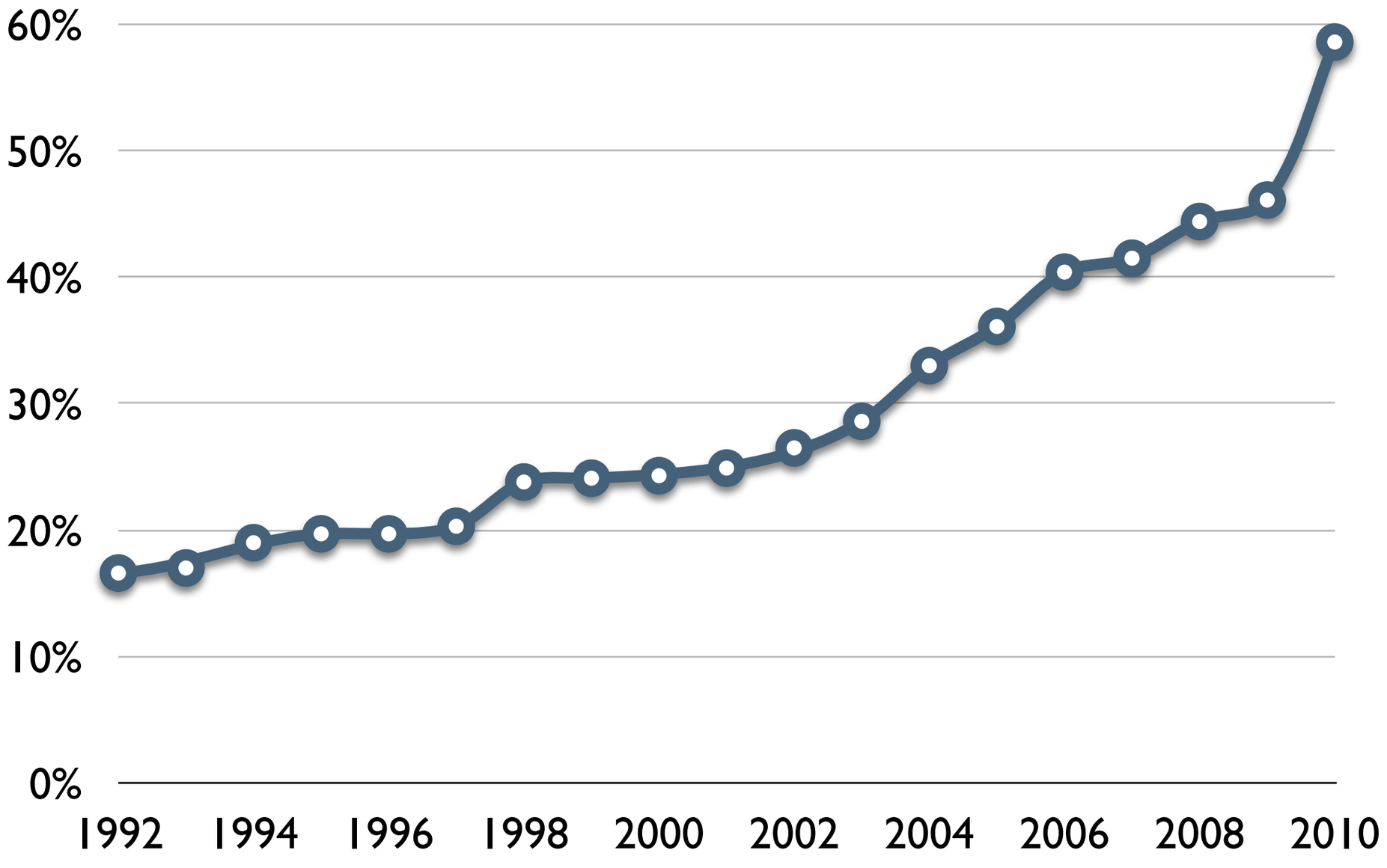
Source: Australian Government, "Characteristics of Disability Support Pension Recipients, June 2011."

New Cases of Disability in Denmark Due to Mental Illness



Source: Danish government, The Appeals Board, Statistics on Early Retirement.

Percentage of All New Disability Cases in Sweden That Are Due to Mental Illness



Source: OECD. Mental Health and Work: Sweden, 2013.

And Finally, a Diagnostic Manual that Lacks Validity

"When I graduated a generation ago, I accepted *DSM IV* as if it were the truth. I trusted that my elders would put the truth first, and then compromise for practical purposes where they had no truths to follow. It took me two decades to realize a painful truth, spoken now frankly by those who gave us *DSM III* when Ronald Reagan was elected, and by those who gave us *DSM IV* when Bill Clinton was president: the leaders of those DSMs don't believe there are scientific truths in psychiatric diagnosis —only mutually agreed upon falsehoods. They call it reliability."

—Nassir Ghaemi, Tufts Medical School Department of Psychiatry, 2013.

Anatomy of a Failed Paradigm of Care

- The biology of mental disorders remains unknown.
- Psychiatric drugs induce the very abnormalities hypothesized to cause mental disorders (oppositional tolerance).
- Over the long-term, antidepressants and other psychiatric drugs increase the chronicity of the disorders they are supposed to treat.
- Antidepressants and stimulants increase the risk that a person will turn "bipolar," which is fueling the increase in the number of disabled mentally ill.
- Since the publication of DSM III, the number of people disabled by mental illness in the United States and other developed countries has soared.
- The DSM categories lack "validity".